What I find most interesting about feline diabetes

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During the last years our diabetes group in Zurich has investigated three main topics: (1) characterization of β-cell damage in feline diabetes, (2) treatment protocols to increase remission rates and (3) tools for diabetes monitoring.

(1) The classification of diabetes mellitus in cats has traditionally followed the scheme used in humans, where the main categories are type 1 diabetes, type 2 diabetes, specific types of diabetes due to other causes and gestational diabetes. Type 2 diabetes is the most common form and is due to a progressive insulin secretory defect on the background of insulin resistance (ADA, 2015). It is currently assumed, that a large percentage of diabetic cats suffer from a type 2-like diabetes mellitus. So far, very little work has been done on β-cell function and insulin secretion in cats with natural development of diabetes. The big question: "What exactly leads to β-cell failure under natural conditions?" is unanswered until today. It is known for quite some time that chronic hyperglycemia has damaging effects on β-cells, known under the umbrella term of glucotoxicity. We recently investigated glucose-induced lesions in healthy cats by maintaining blood glucose constantly between 25 – 30 mmol/l for a period of 10 days. Already 2 days after the beginning of the glucose clamp insulin levels started to decline and dropped to close to the detection limit of the assay. After 10 days of hyperglycemia β-cells were reduced by 50% compared to controls. Islet cells showed apoptotic features and were caspase-3 (a marker for apoptosis) positive. Additionally, hyperglycemia induced a systemic inflammatory response, characterized by an increase of α1-acid glycoprotein (Zini et al, 2009). The concept of glucotoxicity is very important to understand because immediate treatment of diabetes may reverse (at least in part) the negative effects of glucose on β-cells and increase the chance of diabetic remission. However, it is clear, that glucotoxicity is a secondary event, because hyperglycemia becomes apparent only after β-cells start to fail. One long-known hypothesis concerns β-cell destruction by amyloid deposition. Only cats, humans and nonhuman primates have an amyloidogenic amino acid structure of amylin, which is stored together with insulin in secretory vesicles and is co-secreted with insulin. Interestingly, however, amyloid deposits were similar in diabetic cats and matched control cats. Neither the frequency of amyloid deposits (54% of diabetic cats, 40% of controls) nor the extent of amyloid deposition differed between the groups (Zini et al, 2016). As result of this study, we hypothesize that amyloid deposits within the islets (i.e. around the β-cells) are not the primary cause of β-cell failure. Studies are underway to investigate the role of so-called toxic oligomers of amylin within the β-cells in the pathogenesis of feline diabetes.

(2) Remission of diabetes is defined as a situation in which clinical signs of diabetes disappear, blood glucose concentration normalizes and insulin treatment can be discontinued. In human medicine, the duration of normoglycemia has to be at least one year to be labelled remission (Buse et al, 2009). In cats, there is not yet an agreement of the time period. In Zurich we use a cut-off of 4 weeks as criterion, i.e. the disease-free interval has to last for a minimum of 4 weeks before the diabetes is considered to be in remission (Sieber-Ruckstuhl et al, 2008). Remission is increasingly recognized and it is assumed that good glycemic control improves β-cell function most likely due to abolishment of the damaging effects of high blood glucose on β-cell function. Cats which do not experience diabetic remission may be in a more advanced stage of their disease with more pronounced β-cell loss or suffer from substantial concurrent disease. Diabetic remission most often occurs during the first three to four months

of therapy. Consequently, the first months after diagnosis is the most important time during management of diabetes. We recently investigated, if initial constant intravenous insulin application (insulin aspart) over 1 week decreases subsequent insulin requirements and increases remission rate. Overall, 87% of cats of the IV group achieved good metabolic control or diabetic remission compared to 57% in the group of cats receiving insulin glargine BID. Insulin dose given during the 6-month follow-up was significantly lower in the IV group. We attributed the beneficial effect to improved β-cell function similar to what has been shown in human diabetics treated with initial intensive IV insulin protocols (Hafner et al, 2014). As this approach is labour and cost intensive other treatment modalities are under investigation. A similar beneficial effect was found in a pilot study, when a GLP-1 analogue (Exenatide extended release SC once per week) was added to our standard protocol (insulin glargine BID, low-carbohydrate diet). 93% of the insulin + GLP-1 group achieved good metabolic control or diabetic remission, compared to 67% in the insulin only group (Riederer et al, 2016). Other investigators have shown that remission rates in diabetic cats treated with insulin glargine or detemir and low-carbohydrate diet are high when glucose targets are set very low (Roomp and Rand, 2009 and 2012; Nack and DeClue, 2014). The challenge for the future will be to find treatment protocols which are safe (i.e. avoid hypoglycaemia) and give the greatest benefit for the patient (i.e. achieve high remission rates).
(3) The fine-tuning of therapy requires measurement of blood glucose and the generation of blood glucose curves. The first manuscript on capillary blood sampling (Wess and Reusch, 2000) was very difficult to get published, because the editor thought that owners would never do blood sampling on their pets. In the meantime, home-monitoring (HM) developed into a routinely used monitoring tool. However, HM is not without challenges: variability of BGC is high (Alt et al, 2007), opinions on frequency of monitoring differ largely and quality control of the glucometer is a continuous concern. To overcome some of the problems with traditional HM we recently validated a continuous glucose monitoring system (CGMS) for use at home (Salesov et al, submitted). The first series of results in diabetic cats are promising.

References

ADA, *Diabetes Care* 38(Suppl. 1), 2015; Alt N et al., *J Am Vet Med Assoc* 230(7), 2007; Buse et al, *Diabetes Care* 32(11), 2009; Hafner et al, *J Vet Intern Med* 28(6), 2014; Nack R and DeClue AE, *Vet Quart* 34(3), 2014; Riederer A et al., *J Vet Intern Med* 30, 2016; Roomp K and Rand J, *J Feline Med Surg* 11, 2009; Roomp K and Rand J, *J Feline Med Surg* 14, 2012; Salesov, submitted; Sieber-Ruckstuhl NS et al., *J Vet Intern Med* 22(6), 2008; Wess G and Reusch C, *J Small Anim Pract* 41(2), 2000; Zini E et al., *Diabetologia* 52(2), 2009; Zini E et al., *Vet Pathol* 53(1), 2016.